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ORIGINAL REPORT

Molecular Profiling and Targeted Therapy for Advanced Thoracic Malignancies: A Biomarker-Derived, Multiarm, Multihistology Phase II Basket Trial

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ABSTRACT

Purpose
We conducted a basket clinical trial to assess the feasibility of such a design strategy and to independently evaluate the effects of multiple targeted agents against specific molecular aberrations in multiple histologic subtypes concurrently.

Patients and Methods
We enrolled patients with advanced non–small-cell lung cancer (NSCLC), small-cell lung cancer, and thymic malignancies who underwent genomic characterization of oncogenic drivers. Patients were enrolled onto a not-otherwise-specified arm and treated with standard-of-care therapies or one of the following five biomarker-matched treatment groups: erlotinib for *EGFR* mutations; selumetinib for *KRAS*, *NRAS*, *HRAS*, or *BRAF* mutations; MK2206 for *PIK3CA*, *AKT*, or *PTEN* mutations; lapatinib for *ERBB2* mutations or amplifications; and sunitinib for *KIT* or *PDGFRA* mutations or amplification.

Results
Six hundred forty-seven patients were enrolled, and 88% had their tumors tested for at least one gene. *EGFR* mutation frequency was 22.1% in NSCLC, and erlotinib achieved a response rate of 60% (95% CI, 32.3% to 83.7%). *KRAS* mutation frequency was 24.9% in NSCLC, and selumetinib failed to achieve its primary end point, with a response rate of 11% (95% CI, 0% to 48%). Completion of accrual to all other arms was not feasible. In NSCLC, patients with *EGFR* mutations had the longest median survival (3.51 years; 95% CI, 2.89 to 5.5 years), followed by those with *ALK* rearrangements (2.94 years; 95% CI, 1.66 to 4.61 years), those with *KRAS* mutations (2.3 years; 95% CI, 2.3 to 2.17 years), those with other genetic abnormalities (2.17 years; 95% CI, 1.3 to 2.74 years), and those without an actionable mutation (1.85 years; 95% CI, 1.61 to 2.13 years).

Conclusion
This basket trial design was not feasible for many of the arms with rare mutations, but it allowed the study of the genetics of less common malignancies.

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INTRODUCTION

Traditionally, the management of patients with cancer and clinical trials in oncology have relied on tumor histopathology.[1,2] However, analyses of genomic alterations in multiple tumor types have led to the following two fundamental observations: tumors originating in the same organ or tissue are genetically heterogeneous,[3] and similar patterns of genomic alterations may be observed in tumors from different tissues of origin.[4,5] Furthermore, it has become clear that some of these genetic aberrations may have a significant impact on the management and prognosis of patients with cancer.[6-8] As a result, the use of genomic biomarkers to individualize cancer treatments has gained widespread acceptance in specific subsets of molecularly selected patients.[7,9,10] Genetic heterogeneity and the presence of similar genetic alterations across different cancer types represent both a clinical challenge and an opportunity to design new therapeutic protocols based on the genomic traits of tumors.[11,12] However, the prevailing clinical trial design paradigms are still primarily based on tumor histopathology and were originally developed to test

nontargeted cytotoxic drugs in a wide range of molecularly unselected patients.[13-15] Hence, it has become increasingly more complex to efficiently evaluate the clinical relevance of the growing number of cancer biomarkers and available targeted therapies.[16-18] Thus, new clinical trial design strategies are needed.[19-24] One approach is the so-called basket trial design, the goal of which is to investigate the effects of targeted agents against specific molecular aberrations across multiple histologic subtypes at the same time.[25]

Here, we report the results of the CUSTOM (Molecular Profiling and Targeted Therapies in Advanced Thoracic Malignancies) trial (ClinicalTrials.gov identifier: NCT01306045). This trial aimed to identify molecular biomarkers and determine their frequency and clinical relevance in patients with advanced non–small-cell lung cancer (NSCLC), small-cell lung cancer (SCLC), and thymic malignancies (TM) and to evaluate the efficacy of multiple targeted therapies in specific molecular subsets of patients.

PATIENTS AND METHODS

Molecular Profiling

The institutional review boards at the National Cancer Institute and Oregon Health and Science University approved the study before initiation of research activities. We prospectively enrolled patients with histologically confirmed recurrent or advanced NSCLC, SCLC (including lung neuroendocrine tumors[26]), or TM to undergo molecular profiling and long-term follow-up (Data Supplement and Appendix Fig A1, online only). Tumor samples were screened concurrently for a core set of genetic alterations that were used for experimental arm enrollment decisions and an exploratory set of molecular analyses. The core set included mutations in *AKT1*, *BRAF*, *EGFR*, *ERBB2*, *HRAS*, *KIT*, *KRAS*, *NRAS*, *PDGFRA*, *PIK3CA*, and *PTEN* and gene amplification in *ERBB2*, *PIK3CA*, and *PDGFRA*. All core assays were performed on paraffin-embedded tumor samples in Clinical Laboratory Improvement Amendments–certified laboratories. The presence of anaplastic lymphoma kinase (*ALK*) gene rearrangements and other potentially actionable mutations in 224 cancer-related genes was assessed with exploratory purposes.

Experimental Treatments

Patients with an *EGFR* mutation were screened for treatment with erlotinib, an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor. Patients with *KRAS*, *HRAS*, *NRAS*, or *BRAF* mutations were screened for treatment with selumetinib, a MEK (MAPK-ERK kinase) inhibitor. Patients with mutations in *PIK3CA*, *AKT1*, or *PTEN* or amplification of *PIK3CA* were screened for treatment with MK2206, an AKT inhibitor. Patients with mutation or amplification of *ERBB2* were screened for treatment with lapatinib, an ErbB2 inhibitor. Patients with mutations in *KIT* or *PDGFRA* or amplification of the latter were screened for treatment with sunitinib, a multitargeted tyrosine kinase inhibitor. Patients who did not harbor mutations in the aforementioned genes or who otherwise did not

Table 1. Patient Demographics and Clinicopathologic Characteristics

Characteristic	NSCLC		SCLC*		Thymic Malignancy		Total	
	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
Total	481	74.3	68	10.51	98	15.147	647	100
Age, years								
18-39	13	3	0	0	17	17	30	5
40-64	253	53	43	63	55	56	351	54
> 65	215	45	25	37	26	27	266	41
Sex								
Male	232	48	35	51	50	51	317	49
Female	249	52	33	49	48	49	330	51
Race/ethnicity								
White	384	80	60	88	76	78	520	80
Black or AA	39	8	2	3	9	9	50	8
Asian	42	9	4	6	10	10	56	9
Other	8	2	1	1	2	2	11	2
Hispanic	9	2	1	1	1	1	11	2
Non-Hispanic	472	98	67	99	97	99	636	98
ECOG performance status								
0	75	16	7	10	13	13	95	15
1	322	67	43	63	77	79	442	68
2	64	13	12	18	7	7	83	13
3-4	20	4	6	9	1	1	27	4
Histologic feature of tumor								
Adenocarcinoma	363	75	0	0	0	0	363	56
Squamous cell carcinoma	64	13	0	0	0	0	64	10
Small cell*	0	0	65	96	0	0	65	10
Thymoma	0	0	0	0	41	42	41	6
Thymic carcinoma	0	0	0	0	48	49	48	7
Other	54	11	3	4	9	9	66	10
Smoking history								
Never-smokers	148	31	5	7	NA	NA	153	24
Current or former smokers	333	69	63	93	NA	NA	396	61

Abbreviations: AA, African American; ECOG, Eastern Cooperative Oncology Group; NA, not applicable; NSCLC, non–small-cell lung cancer; SCLC, small-cell lung cancer.
*Patients included in the SCLC category (n = 68) included 65 patients with a clearly histologically defined SCLC and three patients (other) whose tumors were classified as lung neuroendocrine tumor.

meet eligibility criteria for enrollment onto the targeted treatment arms were enrolled onto a not-otherwise-specified arm and were treated with either standard-of-care therapies or enrolled onto other experimental clinical trials.

Statistical Considerations

On the basis of the molecular profiling results, patients could be assigned in a nonrandomized fashion to one of five specific treatments within each tumor type (NSCLC, SCLC, and TM), adding up to 15 treatment arms. Each of these arms was considered independent and conducted as a phase II trial using an optimal two-stage design.[27] It was hypothesized that the patient selection based on molecular alterations would result in a high objective response rate (ORR). In all arms, with the exception of *EGFR* mutant NSCLC, the trial was conducted to rule out an unacceptably low 10% ORR in favor of 40%. The *EGFR* mutant NSCLC arm aimed to rule out an unacceptably low 30% ORR ($p0 = 0.30$) in favor of 60% ($p1 = 0.60$), based on prior reports.[6,9,28] Kaplan-Meier curves for progression-free survival (PFS) and overall survival (OS) from the time of treatment arm enrollment were calculated. In addition, OS curves were calculated from the time of diagnosis for all patients with NSCLC enrolled onto the study.

RESULTS

Patient Characteristics

From February 2011 to December 2012, 647 patients were enrolled and underwent molecular profiling (Table 1). The most common histologic subtypes were lung adenocarcinoma (n = 363, 56%), lung squamous cell carcinoma (n = 64, 10%), and SCLC (n = 65, 10%). For molecular profiling, archival tissue was used in 474 patients (73%), and a new fresh biopsy was obtained in 172 patients (27%). The biopsy procedures were well tolerated, and the frequency of grade 3 or 4 related complications was 3% (Appendix Table A1, online only). A total of 569 patients (88%) had at least one molecular analysis that was successfully performed. Of these, 257 patients (45%) harbored a genetic abnormality in at least one of the core genes tested, and 23 patients (4%) harbored multiple genetic abnormalities (Fig 1). The frequencies of the most commonly mutated genes in lung cancer are shown in Figure 2 and Table 2. Of the patients harboring genetic abnormalities in the core genes, 212 patients (82%) were considered screen failures (Appendix Table A2, online only), and 45 patients (18%) were enrolled onto one of the 15 treatment arms.

EGFR *Mutations and Erlotinib*

EGFR mutations were detected in 88 (22.1%) of 398 patients with NSCLC, one (2%) of 51 patients with SCLC, and one (1.1%) of 92 patients with TMs. These mutations were found predominantly in adenocarcinomas (n = 84) and in never-smokers (43.1%). In NSCLC, 84.1% of the *EGFR* mutations (n = 74) were known to be erlotinib

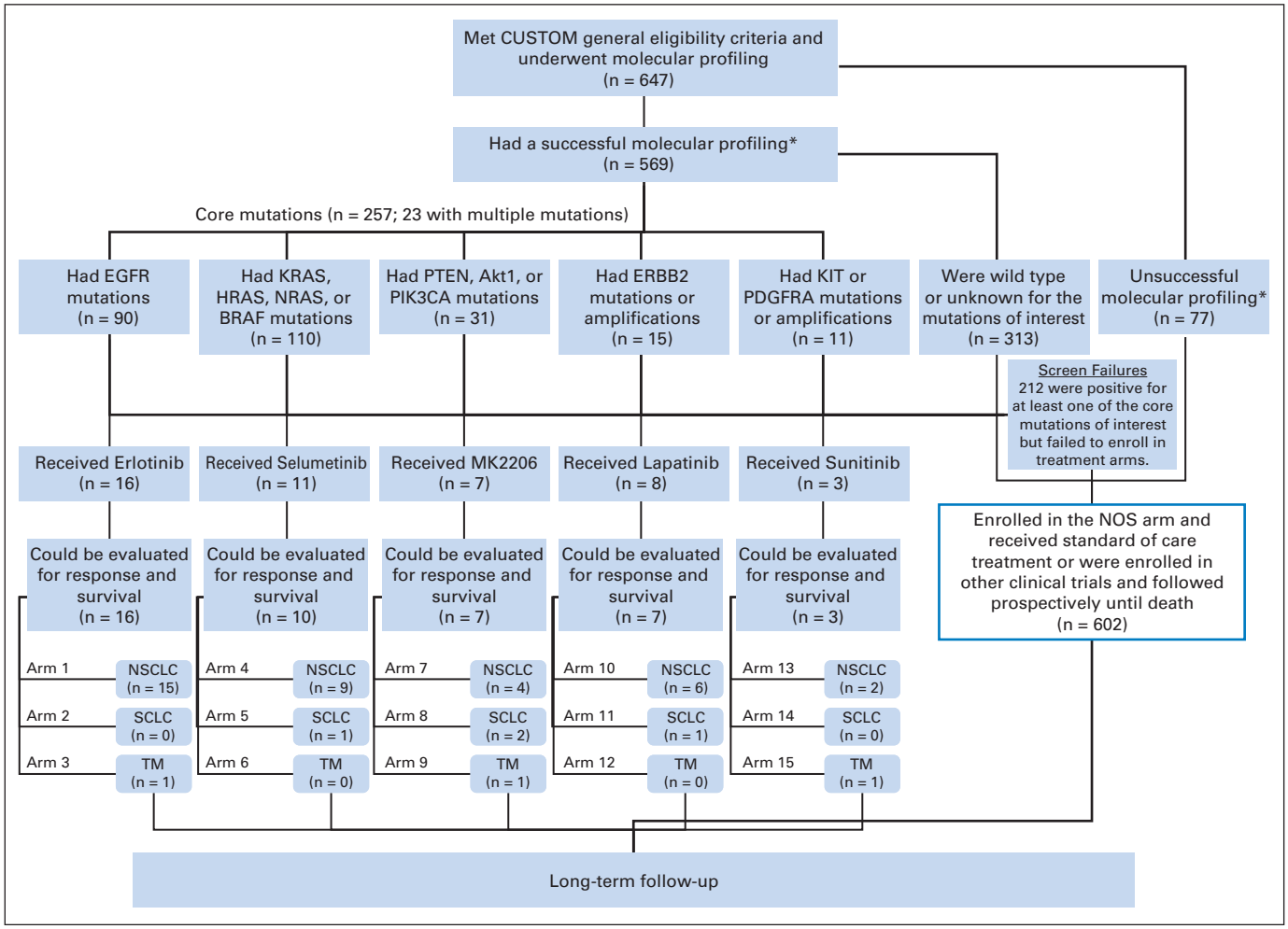

Fig 1. Flow diagram of patient population and treatment assignments. EGFR, epidermal growth factor receptor; NOS, not otherwise specified; NSCLC, non–small-cell lung cancer; PDGFRA, platelet-derived growth factor receptor alpha; SCLC, small-cell lung cancer; TM, thymic malignancy. (*) Successful molecular profiling was defined as having at least one core molecular analysis successfully performed.

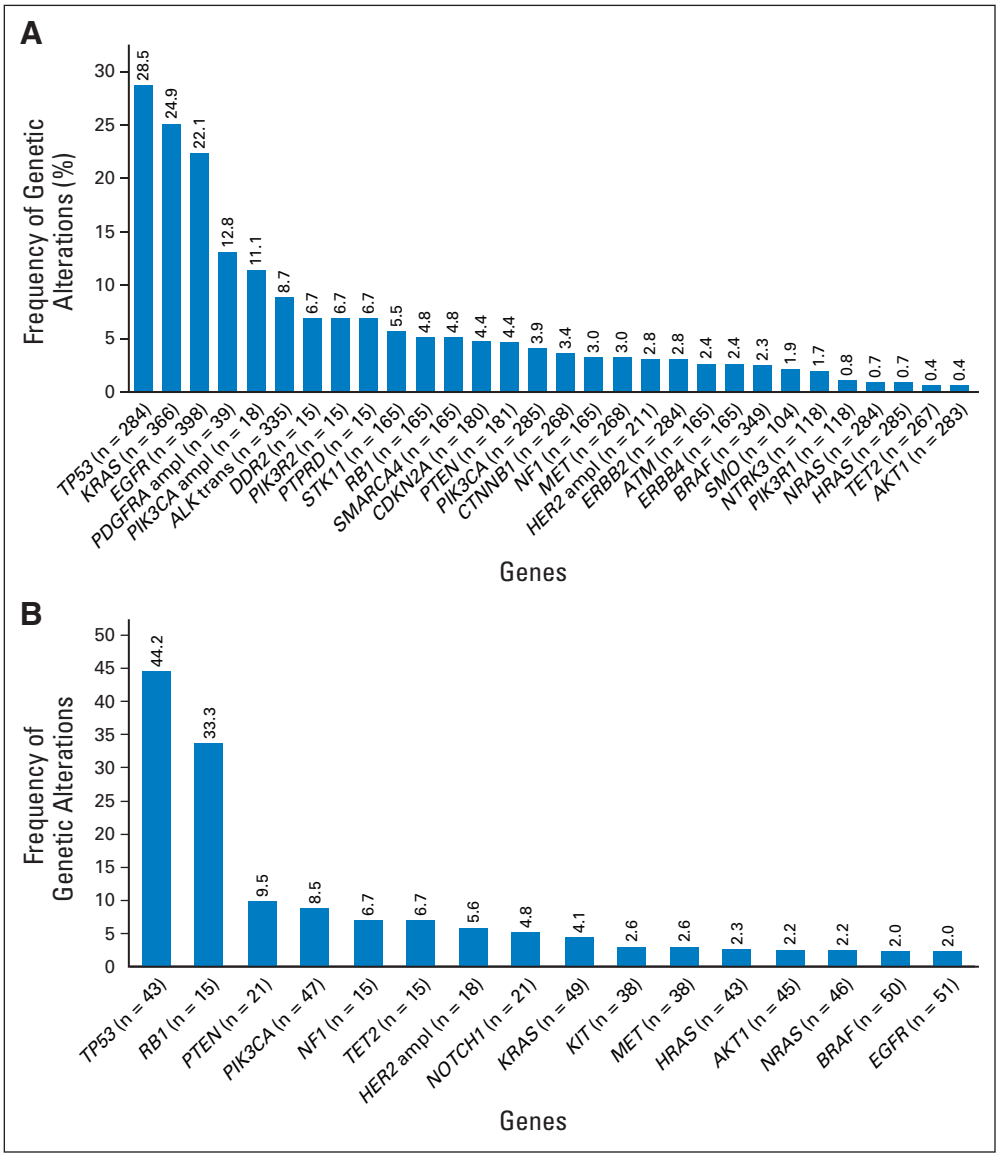

Fig 2. Frequency of genetic abnormalities in (A) non–small-cell lung cancer and (B) small-cell lung cancer.

sensitive (exon 19 deletions and L858R), and in 15 of these patients (20%), a resistant T790M mutation was also present (Appendix Table A3, online only).

Of the 90 patients who harbored mutations in *EGFR*, 16 (15 NSCLCs and one TM) were enrolled onto the erlotinib arm (Fig 1). The main reason for failure to enroll onto this arm was prior erlotinib treatment. Of the 16 patients enrolled onto the erlotinib arm, 15 had evaluable disease. In patients with NSCLC, erlotinib achieved nine partial responses and an ORR of 60% (95% CI, 32.3% to 83.7%; Table 3). The 12- and 24-month PFS rates were 46.7% (95% CI, 24.8% to 69.9%) and 13.3% (95% CI, 3.7% to 37.9%), respectively, and the median PFS time was 11.3 months. At the time of data cutoff on March 1, 2014, the median OS time was 25.7 months, and the 12- and 24-month OS rates were 86.7% (95% CI, 62.1% to 96.3%) and 60.0% (95% CI, 33.0% to 82.1%), respectively. While running this trial, other studies had also confirmed the efficacy of erlotinib in this patient population[6,9,28,29]; therefore, we elected to close this arm before reaching the primary end point. As a result of the low frequency of *EGFR* mutations in SCLC and TM, complete accrual to the erlotinib arm for these tumor types was considered unfeasible.

The median OS from the time of diagnosis for all 90 patients with NSCLC harboring *EGFR* mutations was 3.51 years (95% CI, 2.89 to 5.50 years), and the 12-, 24-, and 36-month OS rates were 90%, 77%, and 58%, respectively. Survival times for patients with NSCLC harboring *EGFR* mutations were significantly longer compared with all other patients with NSCLC (Fig 3).

RAS/RAF *Mutations and Selumetinib*

Mutations in *KRAS* were detected in 91 (24.9%) of 366 patients with NSCLC and two (4.1%) of 49 patients with SCLC (Table 2). These mutations were found predominantly in patients with lung adenocarcinoma in whom the frequency was 27.4% (77 of 204 patients). In current or former smokers with NSCLC and lung adenocarcinoma, the frequencies of *KRAS* mutations were 33.5% and 40.3%, respectively, whereas in never-smokers, the frequencies were 6.8 and 5.7%, respectively. Mutations in *BRAF* were detected in eight

Table 2. Frequency of Genetic Abnormalities in Lung Cancer

Mutation	NSCLC (screened, n = 481)				SCLC (screened, n = 68)			
	No. of Positive Patients	No. of Patients Successfully Tested	Mutation Frequency (%)		Positive	Successfully Tested (n)	Mutation Frequency (%)	
			Rate	95% CI			Rate	95% CI
AKT1	1	283	0.4	0.00 to 1.95	1	45	2.2	0.06 to 11.77
ALK trans	29	335	8.66	5.87 to 12.20	0	19	0.00	0.00 to 17.65
ATM	4	165	2.42	0.66 to 6.09	0	15	0.00	0.00 to 21.80
BRAF	8	349	2.29	0.99 to 4.47	1	50	2.00	0.05 to 10.65
CDKN2A	8	180	4.44	1.94 to 8.57	0	21	0.00	0.00 to 16.11
CTNNB1	9	268	3.36	1.55 to 6.28	0	38	0.00	0.00 to 9.25
DDR2	1	15	6.67	0.17 to 31.95	0	6	0.00	0.00 to 45.93
EGFR	88	398	22.11	18.13 to 26.51	1	51	1.96	0.05 to 10.45
ERBB2	8	284	2.82	1.22 to 5.47	0	40	0.00	0.00 to 8.81
ERBB4	4	165	2.42	0.66 to 6.09	0	15	0.00	0.00 to 21.80
HER2 ampl	6	211	2.84	1.05 to 6.09	1	18	5.56	0.14 to 27.29
HRAS	2	285	0.70	0.09 to 2.51	1	43	2.33	0.06 to 12.29
KIT	0	269	0.0	0.00 to 1.36	1	38	2.6	0.07 to 13.81
KRAS	91	366	24.86	20.52 to 29.62	2	49	4.08	0.50 to 13.98
MET	8	268	2.99	1.30 to 5.80	1	38	2.63	0.07 to 13.81
NF1	5	165	3.03	0.99 to 6.93	1	15	6.67	0.17 to 31.95
NOTCH1	0	180	0.0	0.00 to 2.03	1	21	4.8	0.12 to 23.82
NRAS	2	284	0.70	0.09 to 2.52	1	46	2.17	0.06 to 11.53
NTRK3	2	118	1.69	0.21 to 5.99	0	29	0.00	0.00 to 11.94
PDGFRA ampl	5	39	12.82	4.30 to 27.43	0	3	0.00	0.00 to 70.76
PIK3CA	11	285	3.86	1.94 to 6.80	4	47	8.51	2.37 to 20.38
PIK3CA ampl	2	18	11.11	1.38 to 34.71	0	1	0.00	0.00 to 97.50
PIK3R1	1	118	0.85	0.02 to 4.63	0	29	0.00	0.00 to 11.94
PIK3R2	1	15	6.67	0.17 to 31.95	0	6	0.00	0.00 to 45.93
PTEN	8	181	4.42	1.93 to 8.52	2	21	9.52	1.17 to 30.38
PTPRD	1	15	6.67	0.17 to 31.95	0	6	0.00	0.00 to 45.93
RB1	8	165	4.85	2.12 to 9.33	5	15	33.33	11.82 to 61.62
SMARCA4	8	165	4.85	2.12 to 9.33	0	15	0.00	0.00 to 21.80
SMO	2	104	1.92	0.23 to 6.77	0	38	0.00	0.00 to 9.25
STK11	9	165	5.45	2.52 to 10.10	0	15	0.00	0.00 to 21.80
TET2	1	267	0.4	0.01 to 2.07	1	15	6.7	0.17 to 31.95
TP53	81	284	28.52	23.34 to 34.15	19	43	44.19	29.08 to 60.12

Abbreviations: ampl, amplification; NSCLC, non–small-cell lung cancer; SCLC, small-cell lung cancer; trans, translocation.

(2%) of 349 patients with NSCLC and one (2%) of 49 patients with SCLC. Mutations in *HRAS* and *NRAS* were present in two (0.7%) of 285 and two (0.7%) of 282 patients with NSCLC, respectively, and one (2.3%) of 43 and one (2.2%) of 46 patients with SCLC, respectively. Only two (2.4%) of 85 patients with TM were found to have an *HRAS* mutation; otherwise, no mutations in the *RAS*/*RAF* genes were found in patients with TMs.

Of the 110 patients with *RAS*/*RAF* mutations, 11 patients (10 with NSCLC and one with SCLC) were enrolled onto the selumetinib treatment arms (Fig 1). In nine evaluable patients with NSCLC, selumetinib monotherapy failed to achieve its primary end point during the first stage, with only one partial response (ORR, 11%; 95% CI, 0% to 48%), a median PFS time of 2.3 months, and median OS time of 6.5 months (Table 3). Because of the low frequency of *RAS*/*RAF* mutations in SCLC and TM, it was considered unfeasible to complete accrual to the selumetinib arms.

The median OS from the time of diagnosis for patients with NSCLC harboring *KRAS* mutations was 2.30 years (95% CI, 1.74 to 3.17 years), and the 12-, 24-, and 36-month OS rates were 77%, 55%, and 45%, respectively.

ERBB2 *Mutation/Amplification and Lapatinib*

ERBB2 mutations were detected in eight (2.8%) of 284 patients with NSCLC, zero of 40 patients with SCLC, and zero of 85 patients with TM. These mutations were primarily found in patients with adenocarcinoma histology (n = 7), and all mutations were insertions in exon 20, as previously described.[30] *ERBB2* amplification was found in six (2.8%) of 211 patients with NSCLC, one (5.6%) of 17 patients with SCLC, and one (1.2%) of 84 patients with TM (Table 2). Of the 15 patients with *ERBB2* alterations, eight patients (seven with NSCLC and one with SCLC) received lapatinib (Fig 1). Because of the low frequency of *ERBB2* alterations, it was considered unfeasible to complete accrual to the lapatinib arms in all cohorts. No responses were observed in any of the patients enrolled.

PIK3CA, AKT, *and* PTEN *Abnormalities and MK2206*

PIK3CA mutations were found in 11 (3.9%) of 285 patients with NSCLC, four (8.5%) of 47 patients with SCLC, and two (2.4%) of 85 patients with TM. In patients with NSCLC, these mutations were primarily found in patients with adenocarcinoma histology (n = 9). In addition, *PIK3CA* amplification was found in two (11.1%) of 18

Table 3. Enrollment and Efficacy Assessments

Cancer and Treatment	No. of Patients Enrolled	No. of Patients Evaluable	PR (No.)	SD (No.)	PD (No.)	ORR (%)
NSCLC						
Erlotinib	15	15	9	5	1	60
Lapatinib	7	6	0	4	2	0
Sunitinib	2	2	0	1	1	0
Selumetinib	10	9	1	4	4	11
MK2206	4	4	0	4	0	0
SCLC						
Erlotinib	0	0	0	0	0	0
Lapatinib	1	1	0	1	0	0
Sunitinib	0	0	0	0	0	0
Selumetinib	1	1	0	0	1	0
MK2206	2	2	0	0	2	0
Thymic malignancies						
Erlotinib	1	1	0	0	1	0
Lapatinib	0	0	0	0	0	0
Sunitinib	1	1	0	1	0	0
Selumetinib	0	0	0	0	0	0
MK2206	1	1	0	1	0	0

Abbreviations: NSCLC, non–small-cell lung cancer; ORR, overall response rate; PD, progressive disease; PR, partial response; SCLC, small-cell lung cancer; SD, stable disease.

patients with NSCLC. Mutations in *AKT1* were observed in one (0.4%) of 283 and one (2.2%) of 45 patients with NSCLC and SCLC, respectively, and in no patients with TM. *PTEN* mutations were found in eight (4.4%) of 181 patients with NSCLC, two (9.5%) of 21 patients with SCLC, and no patients with TM. Of the 28 patients with alterations in the *PIK3CA*/*AKT*/*PTEN* pathway, seven patients were enrolled (four with NSCLC, two with SCLC, and one with TM) in the MK2206 arm. Because of the low frequency of genetic alterations in this pathway, it was considered unfeasible to complete accrual to this treatment arm in all cohorts. No responses were observed in any of the patients enrolled.

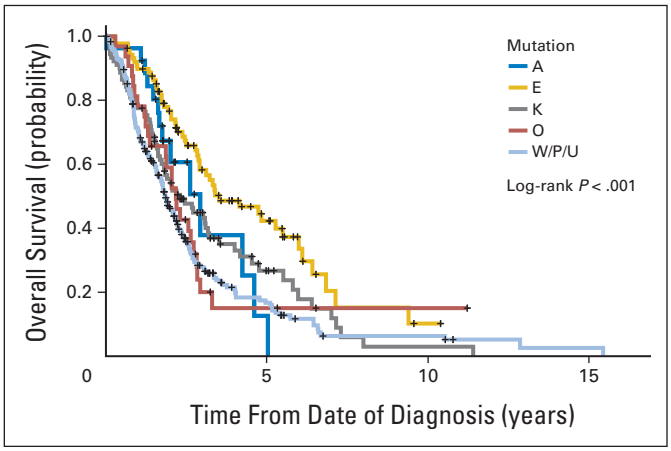

Fig 3. Overall survival in patients with non–small-cell lung cancer stratified by mutation. A, patients harboring *ALK* rearrangements; E, patients harboring *EGFR* mutations; K, patients harboring *KRAS* mutations; O, patients harboring other genetic abnormalities including mutations in *BRAF*, *ERBB2*, *NRAS*, *PIK3CA*, *HRAS*, *NRAS*, *PTEN*, and *ERBB2* amplifications; W/P/U, patients with no mutations found or unsuccessful molecular profiling.

KIT *and* PDGFRA *Genetic Abnormalities and Sunitinib*

KIT mutations were found in one (2.6%) of 38 patients with SCLC, four (4.7%) of 85 patients with TM, and zero of 269 patients with NSCLC. *PDGFRA* mutations were found in one (1.2%) of 85 patients with TM and none of the patients with NSCLC (n = 103) or SCLC (n = 23). *PDGFRA* amplifications were found in five (12.8%) of 39 patients with NSCLC and none of the patients with SCLC (n = 3) and TM (n = 7). Because of the low frequency of *KIT*/*PDGFRA* alterations, it was unfeasible to complete accrual to this treatment arm in all cohorts. Of three patients who were enrolled onto the sunitinib arms, one partial response was observed in a patient with TM (Table 3).

Other Genetic Abnormalities and Outcomes

Rearrangements in *ALK* by fluorescent in situ hybridization break-apart analysis were found in 29 (8.7%) of 335 patients with NSCLC and no patients with SCLC (n = 19) or TM (n = 86; Table 2 and Fig 2). This genetic abnormality was predominately found in patients with lung adenocarcinoma (n = 27), and its frequency was highest among patients who had never smoked (14.3%). The median OS time for patients with NSCLC harboring an *ALK* rearrangement was 2.94 years (95% CI, 1.66 to 4.61 years), and the 12-, 24-, and 36-month OS rates were 96%, 67%, and 38%, respectively. Survival in patients with NSCLC harboring *ALK* rearrangements was significantly better compared with the group of patients in whom no genetic abnormalities were found (Fig 3).

Further analysis in patients with NSCLC showed strong evidence for a survival difference among five molecularly defined patient groups (Fig 3). Patients with *EGFR* mutations had the longest survival times, followed by those with *ALK* rearrangements, *KRAS* mutations, and other genetic abnormalities. Patients without a molecular alteration found in one of the core genes analyzed had the shortest survival times. Treatment-related toxicities of the experimental treatments are listed in Appendix Table A4 (online only).

DISCUSSION

To our knowledge, CUSTOM is the first completed basket clinical trial to investigate the effects of targeted agents against specific molecular aberrations across multiple histologic subtypes at the same time.[15,20,31] A distinctive feature of the protocol design is that it allowed enrollment of patients with multiple histologic subtypes, a nonspecified number of previous therapies, and any organ function or performance status onto the molecular profiling portion of the study. As a result, we were able to enroll 647 patients in only 20 months. Consistent with other reports,[4,5,32] we were able to identify different subgroups of patients who were defined at the molecular level and for whom response to treatment and survival were significantly different from the overall population (ie, patients harboring *EGFR*[6,9,28]). In addition, we were able to conduct exploratory molecular profiling analyses in uncommon cancers such as TMs and those with limited actionable genetic aberrations such as SCLC that pointed out the significant molecular heterogeneity of the different histopathology-based cancer categories and suggesting, as in previous reports,[4,5,33-35] that histology is an important predictor of the presence or absence of specific molecular biomarkers.

A second distinctive feature of the trial's design is that each treatment arm functioned as an independent phase II trial[27] aiming at

identifying drugs with response rates of more than 40%. Thus, only a small number of patients were needed to meet the primary end point of each arm. For instance, with only 15 patients with NSCLC harboring *EGFR* mutations enrolled onto the erlotinib treatment arm, this compound achieved promising results with nine partial responses and an ORR of 60%. However, with only nine evaluable patients with NSCLC harboring *KRAS* or *BRAF* mutations enrolled onto the selumetinib monotherapy arm over a period of 9 months, this drug did not meet its primary end point, with an ORR of 11%. These results are consistent with other clinical trials[9,36,37] and demonstrate the potential capability of identifying compounds with high and low clinical activity in small cohorts of molecularly selected patients by using the CUSTOM's clinical trial design.

However, our study has significant limitations, including the relatively small number of genes that were analyzed, the lack of testing of some important targets in lung cancer (ie, *ROS1* rearrangements[38,39] and *RET* fusions,[40-42] among many others), and the fact that the molecular tests performed in each patient varied significantly as a result of the heterogeneity of the samples available for testing and the capabilities of the local testing laboratories. Furthermore, there was a significant delay in the availability of some of the core molecular profiling results, which had a significant impact in treatment arm enrollment (Table A2). In addition, the study was conducted at only two centers, which limited our ability to identify enough patients to successfully complete accrual to experimental arms in patients with rare histologic subtypes (ie, SCLC and TM) and patients in whom the molecular abnormalities were present at low frequencies (ie, *ERBB2*, *PIK3CA*, *PTEN*, *AKT*, *KIT*, *PDGFRA*). In contrast, even though we identified a large number of patients with NSCLC with *EGFR* and *RAS*/*RAF* mutations potentially eligible for enrollment, the previous use of erlotinib and the early closure of the selumetinib arm accounted for 68% of all screen failures. As a result, only 18% of potentially eligible patients harboring core genetic abnormalities were enrolled onto treatment arms, and it was not feasible to complete accrual to 13 of the 15 available arms. The lack of an adaptive design, such as that used in Investigation of Serial Studies to Predict Your Therapeutic Response With Imaging And Molecular Analysis 2 (I-SPY2)[22] or in the new Southwest Oncology Group 1400 study, in which new treatment arms can be incorporated as new drugs or molecular targets become available, was a significant weakness of CUSTOM. In retrospect, such an adaptive design would have allowed us to incorporate new arms for molecular targets that have become important (ie, *ROS1* rearrangements[38,39] and *RET* fusions,[40-42] among many others) since the beginning of the study. In addition, such a strategy would have allowed us to add new drugs to replace selumetinib after it failed to achieve its primary end point or erlotinib once it became widely used in *EGFR*-mutant NSCLC, allowing us to enroll more patients with *RAS*/*RAF* or *EGFR* mutations in the treatment arms of the study.

Thus, although it was feasible to enroll a large number of patients and perform molecular profiling analyses at a high success rate in an innovative basket trial, the CUSTOM design seems to be unfeasible in its current form given the rarity of the selected genetic abnormalities in the populations under study. New basket trial designs should consider including a larger number of institutions and an adaptive design to successfully conduct such studies.

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Disclosures provided by the authors are available with this article at www.jco.org.

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GLOSSARY TERMS

anaplastic lymphoma kinase (ALK): an enzyme that, in humans, is encoded by the *ALK* gene.

epidermal growth factor receptor (EGFR): a member of a family of receptors (HER2, HER3, HER4 are other members of the family) that binds to the EGF, TGF-α, and other related proteins, leading to the generation of proliferative and survival signals within the cell. EGFR (also known as HER1) also belongs to the larger family of tyrosine kinase receptors and is generally overexpressed in several solid tumors of epithelial origin.

ErbB: also called the human epidermal growth factor receptor (HER). ErbB belongs to the epidermal growth factor receptor (EGFR) family. ErbB1 (EGFR/HER1), ErbB2 (HER2), ErbB3 (HER3), and ErbB4 (HER4) are the four members that comprise this receptor family. See HER2 *neu* (human epidermal growth factor receptor 2).

***K-RAS*:** the gene that encodes K-RAS, a protein that is a member of the small GTPase superfamily, in which a single amino acid substitution results in an activating mutation. Alternative splicing gives rise to variants encoding two isoforms that differ in the C-terminal region.

MEK (MAPK-ERK kinase): a protein kinase activated by c-Raf through phosphorylation of specific serine residues. Activation of ERK by activated MEK may lead to translocation of ERK to the nucleus, resulting in the activation of specific transcription factors.

molecular profiling: a discipline that uses a variety of approaches to generate a global view of mRNA, protein patterns, and DNA alterations in various cell types. Thus, molecular profiles of disease processes may be seen as distinct from normal cells, and therapeutic approaches may be tailored on the basis of molecular profiles.

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Appendix

Table A1. New Biopsy-Related Complications and Success Rate

	Grade 1		Grade 2		Grade 3		Grade 4		Total	
Complication	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
Pneumothorax	5	3	2	1	2	1	0	0	9	6
Pulmonary hemorrhage	0	0	3	2	1	1	0	0	4	3
Vocal cord paralysis	1	1	0	0	0	0	0	0	1	1
Dyspnea	1	1	0	0	0	0	0	0	1	1
Hypoxia	0	0	1	1	1	1	0	0	2	1
Atrial fibrillation/supraventricular tachycardia	0	0	2	1	0	0	0	0	2	1
Bradycardia	0	0	1	1	0	0	0	0	1	1
Total	7	5	9	6	4	3	0	0	20	13

NOTE. A total of 172 new biopsies were performed. Biopsies provided adequate tissue for all proposed core analyses in 148 patients (86%), were inadequate for any analysis in 19 patients (11%), and were adequate only for part of the analyses in five patients (3%).

Table A2. Reasons for Screen Failure

Arm	No. of Patients	%
EGFR mutation/erlotinib arms		
Arm 1: NSCLC		
NSCLC + *EGFR* mutation patients	88	100
Enrolled onto experimental treatment arm	15	17
Screen failure reasons		
Erlotinib treatment before enrollment	51	58
Not eligible as a result of resistant mutation	6	7
On other treatment without disease progression	7	8
Poor performance status/died without erlotinib treatment	1	1
Refused enrollment and treatment with experimental treatment	1	2
Molecular profiling results delayed/not available until after study closure	4	5
Reason not documented/lost to follow-up	3	3
Arm closed to enrollment	0	0
Total	88	
Arm 2: SCLC		
SCLC + *EGFR* mutation patients	1	100
Enrolled onto experimental treatment arm	0	0
Screen failure reasons		
Erlotinib treatment before enrollment	0	0
Not eligible as a result of resistant mutation	0	0
On other treatment without disease progression	0	0
Poor performance status/died without erlotinib treatment	0	0
Refused enrollment and treatment with experimental treatment	0	0
Molecular profiling results delayed/not available until after study closure	1	100
Reason not documented/lost to follow-up	0	0
Arm closed to enrollment	0	0
Total	1	
Arm 3: thymic malignancies		
Thymic malignancy + *EGFR* mutation patients	1	100
Enrolled onto experimental treatment arm	1	100
Screen failure reasons		
Erlotinib treatment before enrollment	0	0
Not eligible as a result of resistant mutation	0	0
On other treatment without disease progression	0	0
Poor performance status/died without erlotinib treatment	0	0
Refused enrollment and treatment with experimental treatment	0	0
Molecular profiling results delayed/not available until after study closure	0	0
Reason not documented/lost to follow-up	0	0
Arm closed to enrollment	0	0
Total	1	
KRAS, *HRAS*, *NRAS*, or *BRAF* mutation/selumetinib arms		
Arm 4: NSCLC		
NSCLC + *KRAS*, *HRAS*, *NRAS*, or *BRAF* mutation patients	103	100
Enrolled onto experimental treatment arm	10	10
Screen failure reasons		
Selumetinib treatment before enrollment	0	0
Not eligible as a result of resistant mutation	0	0
On other treatment without disease progression	0	0
Poor performance status/died without erlotinib treatment	0	0
Refused enrollment and treatment with experimental treatment	0	0
Molecular profiling results delayed/not available until after study closure	0	0
Reason not documented/lost to follow-up	0	0
Arm closed to enrollment	93	90
Total	103	
Arm 5: SCLC		
SCLC + *KRAS*, *HRAS*, *NRAS*, or *BRAF* mutation patients	5	100
Enrolled onto experimental treatment arm	1	20
Screen failure reasons		
Selumetinib treatment before enrollment	0	0
Not eligible as a result of resistant mutation	0	0

(continued on following page)

Table A2. Reasons for Screen Failure (continued)

Arm	No. of Patients	%
On other treatment without disease progression	0	0
Poor performance status/died without erlotinib treatment	1	20
Refused enrollment and treatment with experimental treatment	0	0
Molecular profiling results delayed/not available until after study closure	0	0
Reason not documented/lost to follow-up	3	60
Arm closed to enrollment	0	0
Total	5	
Arm 6: Thymic malignancies		
Thymic malignancies + *KRAS*, *HRAS*, *NRAS*, or *BRAF* mutation patients	2	100
Enrolled onto experimental treatment arm	0	0
Screen failure reasons		
Selumetinib treatment before enrollment	0	0
Not eligible as a result of resistant mutation	0	0
On other treatment without disease progression	0	0
Poor performance status/died without erlotinib treatment	0	0
Refused enrollment and treatment with experimental treatment	0	0
Molecular profiling results delayed/not available until after study closure	2	100
Reason not documented/lost to follow-up	0	0
Arm closed to enrollment	0	0
Total	2	
PTEN/*AKT1*, *PIK3CA* abnormalities/MK2206 arms		
Arm 7: NSCLC		
Patients with *PTEN*, *AKT1*, or *PIK3CA* abnormalities	22	100
Enrolled onto experimental treatment arm	4	18
Screen failure reasons		
MK2206 treatment before enrollment	0	0
Not eligible as a result of resistant mutation	0	0
On other treatment without disease progression	0	0
Poor performance status/died without erlotinib treatment	0	0
Refused enrollment and treatment with experimental treatment	0	0
Molecular profiling results delayed/not available until after study closure	7	32
Reason not documented/lost to follow-up	11	50
Arm closed to enrollment	0	0
Total	22	
Arm 8: SCLC		
Patients with *PTEN*, *AKT1*, or *PIK3CA* abnormalities	7	100
Enrolled onto experimental treatment arm	2	29
Screen failure reasons		
MK2206 treatment before enrollment	0	0
Not eligible as a result of resistant mutation	0	0
On other treatment without disease progression	0	0
Poor performance status/died without erlotinib treatment	0	0
Refused enrollment and treatment with experimental treatment	0	0
Molecular profiling results delayed/not available until after study closure	2	29
Reason not documented/lost to follow-up	3	43
Arm closed to enrollment	0	0
Total	7	
Arm 9: Thymic malignancies		
Patients with *PTEN*, *AKT1*, or *PIK3CA* abnormalities	2	100
Enrolled onto experimental treatment arm	1	50
Screen failure reasons		
MK2206 treatment before enrollment	0	0
Not eligible as a result of resistant mutation	0	0
On other treatment without disease progression	0	0
Poor performance status/died without erlotinib treatment	0	0
Refused enrollment and treatment with experimental treatment	0	0
Molecular profiling results delayed/not available until after study closure	0	0
Reason not documented/lost to follow-up	1	50
Arm closed to enrollment	0	0
Total	2	

(continued on following page)

Table A2. Reasons for Screen Failure (continued)

Arm	No. of Patients	%
ERBB2 mutations or amplifications/lapatinib arms		
Arm 10: NSCLC		
Patients with *ERBB2* mutations or amplifications	13	100
Enrolled onto experimental treatment arm	7	54
Screen failure reasons		
Lapatinib treatment before enrollment	0	0
Not eligible as a result of resistant mutation	0	0
On other treatment without disease progression	0	0
Poor performance status/died without erlotinib treatment	0	0
Refused enrollment and treatment with experimental treatment	0	0
Molecular profiling results delayed/not available until after study closure	0	0
Reason not documented/lost to follow-up	6	46
Arm closed to enrollment	0	0
Total	13	
Arm 11: SCLC		
Patients with *ERBB2* mutations or amplifications	1	100
Enrolled onto experimental treatment arm	1	100
Screen failure reasons		
Lapatinib treatment before enrollment	0	0
Not eligible as a result of resistant mutation	0	0
On other treatment without disease progression	0	0
Poor performance status/died without erlotinib treatment	0	0
Refused enrollment and treatment with experimental treatment	0	0
Molecular profiling results delayed/not available until after study closure	0	0
Reason not documented/lost to follow-up	0	0
Arm closed to enrollment	0	0
Total	1	
Arm 12: thymic malignancies		
Patients with *ERBB2* mutations or amplifications	1	100
Enrolled onto experimental treatment arm	0	0
Screen failure reasons		
Lapatinib treatment before enrollment	0	0
Not eligible as a result of resistant mutation	0	0
On other treatment without disease progression	0	0
Poor performance status/died without erlotinib treatment	0	0
Refused enrollment and treatment with experimental treatment	0	0
Molecular profiling results delayed/not available until after study closure	0	0
Reason not documented/lost to follow-up	1	100
Arm closed to enrollment	0	0
Total	1	
KIT or *PDGFRA* genetic abnormalities/sunitinib arms		
Arm 13: NSCLC		
Patients with *KIT* or *PDGFRA* genetic abnormalities	5	100
Enrolled onto experimental treatment arm	2	40
Screen failure reasons		
Sunitinib treatment before enrollment	0	0
Not eligible as a result of resistant mutation	0	0
On other treatment without disease progression	0	0
Poor performance status/died without erlotinib treatment	0	0
Refused enrollment and treatment with experimental treatment	0	0
Molecular profiling results delayed/not available until after study closure	3	60
Reason not documented/lost to follow-up	0	0
Arm closed to enrollment	0	0
Total	5	
Arm 14: SCLC		
Patients with *KIT* or *PDGFRA* genetic abnormalities	1	100
Enrolled onto experimental treatment arm	0	0
Screen failure reasons		
Sunitinib treatment before enrollment	0	0
Not eligible as a result of resistant mutation	0	0

(continued on following page)

Table A2. Reasons for Screen Failure (continued)

Arm	No. of Patients	%
On other treatment without disease progression	0	0
Poor performance status/died without erlotinib treatment	0	0
Refused enrollment and treatment with experimental treatment	0	0
Molecular profiling results delayed/not available until after study closure	1	100
Reason not documented/lost to follow-up	0	0
Arm closed to enrollment	0	0
Total	1	
Arm 15: thymic malignancies		
Patients with *KIT* or *PDGFRA* genetic abnormalities	5	100
Enrolled onto experimental treatment arm	1	20
Screen failure reasons		
Sunitinib treatment before enrollment	0	0
Not eligible as a result of resistant mutation	0	0
On other treatment without disease progression	0	0
Poor performance status/died without erlotinib treatment	0	0
Refused enrollment and treatment with experimental treatment	0	0
Molecular profiling results delayed/not available until after study closure	4	80
Reason not documented/lost to follow-up	0	0
Arm closed to enrollment	0	0
Total	5	

Abbreviations: NSCLC, non–small-cell lung cancer; SCLC, small-cell lung cancer.

Table A3. *EGFR* Mutations in Non–Small-Cell Lung Cancer

Mutation	Total No.	%
Exon 19 deletion	34	38.6
Exon 19 deletion + T790M	7	8.0
L858R	25	28.4
L858R + T790M	8	9.1
Other sensitizing	3	3.4
Other sensitizing + resistant	1	1.1
T790 M alone	1	1.1
Other exon 20 insertions	8	9.1
Unknown activity	1	1.1
Subtotal	88	100.0

Table A4. Experimental Treatment–Related Toxicities

Drug and Adverse Event	No. of Patients				
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Lapatinib					
ALT increased	2				
Allergic reaction			1		
Anorexia		1			
AST increased	1				
Creatinine increased	1				
Diarrhea	1				
Dry skin	1				
Fatigue		2			
Flashing lights	1				
Flatulence	1				
Gastroesophageal reflux disease		1			
Hypomagnesemia	1				
Insomnia	1				
Mucositis oral		2			
Nausea	1	1			
Neutrophil count decreased		1			
Pain in extremity	1				
Pneumonitis	1				
Rash acneiform		1			
WBC decreased	1				
Erlotinib					
ALT increased			2		
Allergic reaction		1			
Allergic rhinitis		1			
Alopecia	1	1			
Alkaline phosphatase increased			1		
Anemia		1			
Anorexia	1				
AST increased		1	1		
Blood bilirubin increased		1			
Conjunctivitis		2			
Cough		2			
Diarrhea	2	2			
Dizziness		1			
Dry eye		1			
Dry mouth	1				
Dyspepsia		2			
Erythroderma		1			
Eye disorders, other, specify		3			
GI pain		1			
Gum infection		1			
Hypercalcemia	1				
Hyperhidrosis		1			
Hypertrichosis	1				
Hypoalbuminemia		1			
Hypomagnesemia	1				
Hypophosphatemia		1			
Lymphocyte count decreased	1	3			
Mucositis oral	1				
Nausea		1			
Palmar-plantar erythrodysesthesia syndrome		2			
Papulopustular rash		2			
Paronychia		3			
Periorbital edema		2			
Presyncope		1			
Pruritus		1			

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Table A4. Experimental Treatment–Related Toxicities (continued)

Drug and Adverse Event	No. of Patients				
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Rash acneiform		2			
Rash maculopapular		4			
Skin and subcutaneous tissue disorders, other, specify		1			
Skin infection		1			
Syncope			1		
Watering eyes		2			
WBC decreased	1				
Selumetinib					
ALT increased	2	1			
Alkaline phosphatase increased	1				
Anemia	2	1	1	1	
Anorexia		1			
AST increased	2	1			
Bloating	1				
Blurred vision		1			
Constipation		1			
Creatine phosphokinase increased	1	1	1		
Creatinine increased	1				
Diarrhea	1	1	1		
Dizziness	1				
Dry eye		1			
Dry mouth	1				
Edema face	3	1			
Edema limbs		2			
Esophageal hemorrhage				1	
Eye disorders, other, specify		1			
Fatigue	1	1			
GI disorders, other, specify		1			
Headache	1	1			
Hyperkalemia		1			
Hypernatremia	1				
Hypoalbuminemia	1	3			
Hypokalemia			1		
Hypomagnesemia	2				
Hypophosphatemia		1			
Hypoxia			1		
Lymphocyte count decreased	1	1	1		
Mucosal infection		1			
Mucositis oral			1		
Mucositis oral	1				
Nausea	1	1	1		
Paronychia		1			
Periorbital edema		1			
Peripheral sensory neuropathy	1				
Platelet count decreased	1				
Pruritus		2			
Rash acneiform	3				
Upper respiratory infection		1			
Vomiting	2			1	
WBC decreased	1				
Sunitinib					
Abdominal pain		1			
Arthralgia		1			
AST increased		1			
Constipation		1			
Edema limbs		1			
Fatigue		1			

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Table A4. Experimental Treatment–Related Toxicities (continued)

Drug and Adverse Event	No. of Patients				
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Hypertension			1		
Hypertension		1			
Hypertriglyceridemia			1		
Hypoalbuminemia		1			
Hypophosphatemia		1			
Hypothyroidism		1			
Lymphocyte count decreased		1			
Lymphocyte count decreased		1			
Mucositis oral		1			
Mucositis oral		1			
Neutrophil count decreased		1			
Neutrophil count decreased		1			
Palmar-plantar erythrodysesthesia syndrome		1			
Platelet count decreased			1		
Pruritus		1			
Rash maculopapular		1			
Wound dehiscence			1		
MK2206					
Anemia			1		
Arthritis		1			
Fatigue		2			
Fever		1			
Hyperglycemia			1		
Hypertension		1			
Hypoalbuminemia			1		
Hypophosphatemia			1		
Infections and infestations, other, specify		1			
Mucositis oral		1			
Nausea		1			
Pruritus		1			
Rash maculopapular		1	1		
Urinary tract infection		1			

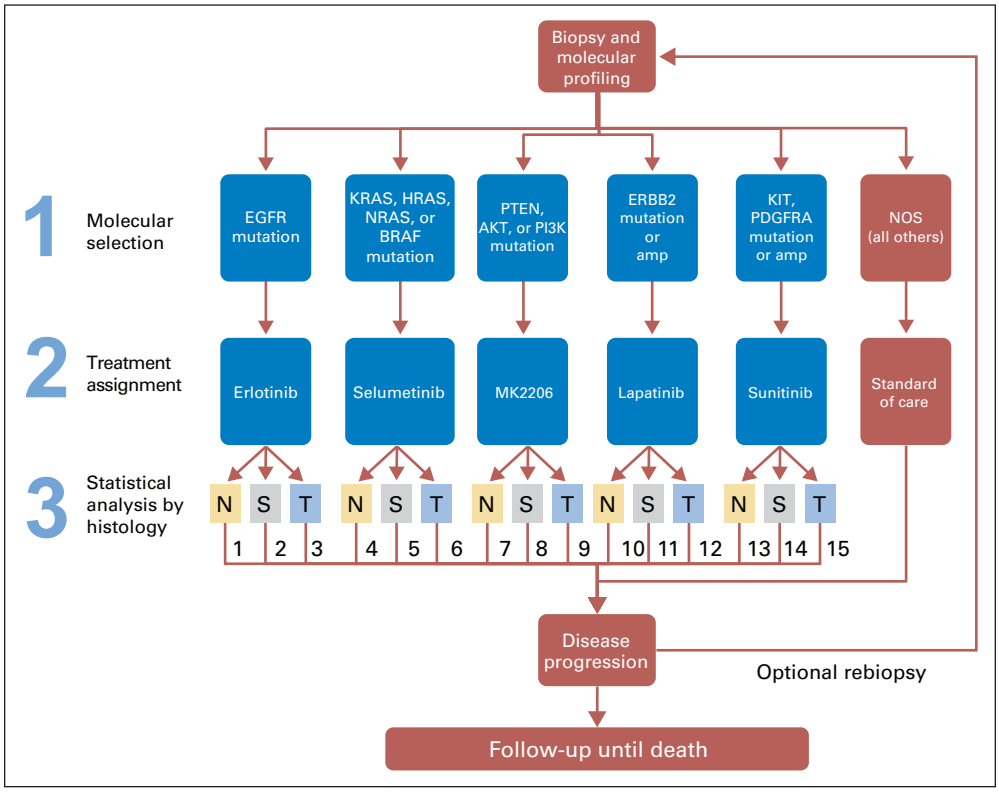

Fig A1. Custom clinical trial design. National Cancer Institute Cancer Therapy Evaluation Program Protocol No. 8639/NCT01306045. EGFR, epidermal growth factor receptor; N, non–small-cell lung cancer; NOS, not otherwise specified; PDGFRA, platelet-derived growth factor receptor alpha; S, small-cell lung cancer; T, thymic malignancies.